ORIGINAL ARTICLES

THE EXPERIMENTAL BASIS OF VACCINE THERAPY.*

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It would be rash indeed to attempt to outline the potential value of vaccine therapy but one may sketch very clearly the historical path that has led to our present method of treating bacterial infections by injecting killed cultures of bacteria. When we later come to consider the rationale of this latest aspect of immunization, that is immunization employed as a therapeutic measure, we shall find ourselves stopping short of ultimate explanation embarrassed not at any failure of the laboratory worker to respond to clinical demand, but by the fact that practice has outstripped theory, and not it is to be feared to the ultimate benefit of practice itself.

The principle of artificial immunization as a measure of prophylaxis is as old as history and may still be found practiced empirically among savage tribes. As soon as a people begins to reason effectively from cause to effect they naturally attempt to create artificially the advantageous condition of acquired immunity which they see has resulted from recovery from a natural disease. The Moors protected their cattle from pleuropneumonia by inoculating them subcutaneously with diseased organs. The South African Vatuas still practice a method of self-immunization against snake bite. The Chinese in early times found they were able to protect themselves from smallpox by inducing a mild form of the disease through placing scabs of variola in the nostrils. This protection by variolization was replaced in 1798 by Jenner's system of vaccination which made use of the novel but fundamental principle of producing immunity through a modified form of the disease.

It was this principle which with the advent of bacteriology, enabled Pasteur to utilize bacterial cultures of diminished virulence in protecting against fowl cholera and anthrax. The observations of Salmon and Smith with hog cholera proved that even killed cultures may be employed for the purpose.

Another and most significant advance in our knowledge of the possibilities of vaccination lay in the discovery of the method of preventing rabies. Owing to the long incubation period in the disease, Pasteur found that an active immunity might be induced by inoculations of rabies virus of increasing potency, if the treatment is inaugurated within fifteen to twenty days after the bite of a rabid animal. This treatment *following* inoculation makes the logical as well as historical step between vaccination for prophylaxis and vaccination in treatment.

The treatment of a disease in active progress by inoculation of the virus of the disease itself was first suggested by Koch in the tuberculin treatment for tuberculosis. Over-enthusiasm of many untrained observers as well as failure to appreciate the real principle involved led to a rapid discrediting of what represents a thoroughly logical though still imperfect method of treating this dread disease. The best observations to-day show that judiciously administered treatment with tuberculin in conjunction with the usual hygienic measures distinctly increases the percentage of cures.

It remained for A. E. Wright, beginning in 1902, to emphasize and to enlarge the scope of active immunization as a method of treatment. Discouraged at the essential failures which were being met with in attempting to treat bacterial infections by passive immunization which had proved so effective in treating certain bacterial intoxications, Wright struck back to the trail which had been so successfully blazed by Pasteur. I shall not at this point criticize Wright's method of approach but may point out at once that his results were not only encouraging but in many points remain practically successful.

Wright's method of treating bacterial infections with killed cultures of the micro-organism concerned, is particularly and primarily efficient with localized lesions, both acute and chronic. The effect produced depends on provoking a generalized reaction of the body which re-inforces the purely local immunity in the tissue surrounding the lesion. The result is commensurate with an increase in antibodies that may be demonstrated in the blood of the patients themselves as well as the more firmly grounded data obtained from active immunization in experimental animals. The extension of this principle of vaccine therapy to the systemic bacterial infections like pneumonia and endocarditis is at once more doubtful practically and more difficult to explain. And at this point we may digress for a moment to criticize Wright's method of attack on this problem of which he has admittedly been the one to prove the importance.

The inauguration of the increasingly successful methods of protecting human beings by vaccination against cholera, plague and typhoid has depended directly on the animal experiments of Pasteur and of Pfeiffer. In the case of antityphoid prophylaxis we owe the best methods of standardizing the vaccine by means of its toxicity for guinea pigs, to Wright himself. And yet in the at best tentative development of vaccine therapy Wright practically omitted experiments on the lower animals and contented himself with experiments in human beings. I am not here concerned with this transition of method from the standpoint of morality so much as from the standpoint of scientific accuracy and expediency. It need scarcely be pointed out to you that animal experimentation offers the only possible method of acquiring the complete series of facts and any consequent deduction as to the cause of biological phenomena. As has just been mentioned the successful treatment of localized infections by vaccination can be explained in a general way *a posteriori* from previous animal experimentation. We know now, however, that Wright's misconception of opsonic activity has only recently been unraveled by careful experimentation in the hands of others who were less eager to offer diagnosis in a few individual cases than to attain to some knowledge of the general principle involved.

When we come then to ask ourselves what results we may expect from Wright's suggestion that we treat, let us say a case of acute endocarditis with inoculations of the micro-organism which is swarm-

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ing in the blood, we find very few facts on which to base a belief. We find ourselves relying solely on what we think has happened in a few apparently similar human cases that have been treated in what we believe to be the same manner. Each one of these cases has been considered apart from any possible control as to what would have happened if no treatment had been given, and each case represents a condition of which we have only the barest conception even under the best conditions in a well-organized hospital. It is true that if we keep our courage up until a hundred cases more or less have done better or worse under this treatment, and if we have made the most minute observations on this series of cases, we may hope to draw some conclusions by comparing them with a similar number of cases treated in other ways and equally well followed. And even then if we find the treatment justified by the results, how may we hope to know from any exact knowledge of the mechanism of the reaction that takes place, how we should modify the treatment to make it more efficient? The plea then is that in applying an experimental method to human beings we should make haste slowly and be patient enough to learn something of the general principle involved, through animal experimentation, before we start to treat individual cases.

In this particular case the experimenter can say little as to the justification for treating a septicemia with bacterial vaccines. It is not easy to see how we can hope to justify it on the ground of provoking any more general reaction as is the case in localized infections. It may, however, be suggested as Smith has done, that the bringing into play of new and unused areas of reaction such as are employed in subcutaneous inoculations might give a reasonable basis of justification in trying this method of treatment.

I think I have sufficiently indicated to you that Wright's method of developing vaccine therapy seems injudicious, although it must be confessed that his popular method has stirred up a general appreciation of the importance of the principle involved. Let us hope that the discrediting of his more visionary ideas on blood coagulation and the opsonic index will not serve to detract from interest in his main thesis of vaccine therapy. In view of these strictures on Wright's method it may seem inconsistent to suggest a possible further improvement of vaccine therapy in human beings. The suggestion, however, is based on results obtained by the methods that have been evolved in active immunization of animals. It has been found that the highest grade of antibacterial immunity is produced by immunizing animals with living rather than with killed bacteria. It has further been found that the best serum to combat an infection like that produced by the bacillus of dysentery is produced by immunizing horses not only against several strains of dysentery bacilli but against the endotoxins of the bacillus. It would be quite feasible to treat human beings with living instead of dead cultures of bacteria at least in the case of those organisms which do not tend to produce generalized infections. We have instances of such inoculation with living cultures in the original and successful method of preventing cholera inaugurated by Ferran. The use of endotoxins as well as whole bacteria would present no danger over the present method. It seems then quite probable from animal experiments that a more efficient therapeutic reaction to bacterial infections might be induced in human beings by the use of living instead of dead bacteria and by the use of endotoxins in conjunction with the bacterial bodies.

I have often wondered what the present state of mind of the clinician may be in respect to the accepted status of immunity from disease. Facts have accumulated so rapidly that they can scarcely be set in order by one who devotes his entire attention to the subject. The balance of evidence has swung between the cells and the body fluids, first Mechnikoff with emphasis on Phagocytosis, then Pfeiffer, Bordet and Ehrlich with accentuation of the humoral aspects, and last the newer viewpoint of Wright lying half way between, and, in reality, linking the two schools together. It seems to me that Wright with his opsonic theory, was a better harmonizer than he knew. Those bodies known as opsonins, which he insisted on with pardonable pride as *sui generis,* seem now to differ very little from the known antibodies (sensitizers or amboceptors) which were really anticipated by Metchnikoff under the name of "stimulins." Facts seem to be tending to prove that the apparently dual lysins evidenced principally in the test tube, may in the body exert their action as a single body combining the attributes of amboceptor, sensitizer and opsonin, and affecting the bacterium in such a way as to make it more readily devoured by the phagocytes which under normal conditions retain the digestive ferment (cytase, alexin, or complement) that is liberated into the serum under artificial condition. Phagocytosis, then, would be the ultimate and essential process, its completeness depending on the degree of sensitization or opsonization produced extracellularly by the antibodies which are the specific results of immunization. This simplified scheme is I believe consistent with the trend of investigations in immunity.

It would seem, in review, that I have been able to offer little help, except perhaps in the line of simplification and clarification, towards the experimental basis of vaccine therapy. The fault lies as I have said in that the experimental basis of vaccine therapy has been inadequate for a safe prognosis. There remains, however, I hope, no doubt in your minds as to the eventual soundness of the method. I have simply ventured to plead for more scientific conservatism in learning its mechanism as tending toward a greater usefulness.

A CLINICAL VIEW OF VACCINE THERAPY.

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In yielding hesitatingly to the request of the program committee to present in the few minutes at our disposal, the clinical side of the vaccine question my decision was determined by the fact, apparent from observation of the cases of many different men, that lax methods in the application and overenthusiasm in the use of vaccines would tend

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